Asymmetric Total Synthesis of (+)- and ent-(−)-Yatakemycin and Duocarmycin SA: Evaluation of Yatakemycin Key Partial Structures and Its Unnatural Enantiomer

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Structure Revision

Structure proposed in 2003 based on spectroscopic studies:

First alternative structure based on NMR comparison and calculation:

Correct structure for (+)-Yatakemycin confirmed through synthesis:

Other members of this class of DNA alkylation agents.


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Retrosynthetic Plan: Asymmetric Synthesis of Core Indole

$\text{ONos}$

$\text{Boc}$

$\text{MeO}_2\text{C}$

$I$

$\text{NHBoc}$

$\text{OBn}$

$(S)$-glycidol 3-nosylate

Previous Racemic Synthesis:

Separation achieved by Chiralcel OD column

$\text{J. Am. Chem. Soc. 1993, 115, 9025.}$
Completion of the Central Fragment

1. Boc₂O, 98%
2. Zn, NH₄Cl, 98%
3. Boc₂O, 95%
4. NIS, 91%

i-PrMgCl
CuI-PBu₃ 69%

MeO₂C−N⁺N₃

MeO₂C−N⁺N₃

Xylenes, reflux

68% + 18% regioisomer

NaH, 96%

Pd/C, HCO₂NH₄ 84%

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Completion of the Left Fragment

1. BnBr, 88%
2. NaClO₂, 97%

1. DPPA; H₂O, 78%
2. TsCl, 89%

1. SnCl₂, 92%
2. Boc₂O, 94%

1. AcOH, 91%
2. Mg, 96%

1. LiOH, 95%
2. EDCI, CH₃SH, 82%
3. HCl, EtOAc, 100%

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Duocarmycin SA

Improved Synthesis of Key Intermediate in Previous Synthesis:

For a review of synthetic studies, see: *Chem. Rev.* 1997, 97, 787.
Yatakemycin

1. EDCI, 58%
2. LiOH, 94%

1. EDCI, 50%
2. DEAD, Ph₃P, 70%

(+)-Yatakemycin
Alkylating agents of various types are used alone or in combination with other agents in the treatment of many cancer patients - alkylation of guanine is a common mechanism of action.

Boger and co-workers were previously able to establish the alkylation of DNA with duocarmycin took place on adenine and this was confirmed to be the mechanism of action for yatakemycin.

Yatakemycin - Adenine Adduct

http://www.paterson.man.ac.uk/groups/carcino/damandrep.jsp
DNA Alkylation: Relative Rates

1. (+)-Yatakemycin

2. (-)-Yatakemycin

3. (+)-CDPI-DSA-CDPI

4. (+)-Duocarmycin SA

5. (+)-N-Boc-DSA

$k_{rel}$ (w836 DNA)

1.0

0.8

0.13

0.1

0.000005
Cytotoxic Activity

1. Yatakemycin

2. CC-1065

3. Duocarmycin A

4. Duocarmycin SA

5. Original yatakemycin structure

6. First alternative structure

L-1210 IC_{50} (pM)

- nat-(+)-yatakemycin: 5
- ent-(−)-yatakemycin: 5
- nat-(+)-enantiomer: 6
- ent-(−)-enantiomer: 6
- nat-(+)-enantiomer: 10
- ent-(−)-enantiomer: 10
- nat-(+)-enantiomer: 10
- ent-(−)-enantiomer: 10
- nat-(+)-enantiomer: 40
- ent-(−)-enantiomer: 600
- nat-(+)-enantiomer: 5
- ent-(−)-enantiomer: 5
- nat-(+)-enantiomer: 70
- ent-(−)-enantiomer: 760
- nat-(+)-enantiomer: 6,000^{16}
- ent-(−)-enantiomer: 60,000^{16}
- nat-(+)-enantiomer: 20^{40}
- ent-(−)-enantiomer: 20^{40}
- nat-(+)-enantiomer: 200^{23}
- ent-(−)-enantiomer: 23,000^{23}

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Conclusions and Future Directions

A second generation, asymmetric synthesis of yatakemycin has been developed that includes a late stage transanular Ar-3’ spriocyclization, regioselective Diels-Alder reaction and a regioselective intramolecular epoxide addition.

With larger quantities of yatakemycin and its analogs available through synthesis, characterization of the yatakemycin-adenine addition adduct was achieved confirming that this represents the predominant (if not exclusive) alkylation event. No guanine N3 or N7 addition was observed in any of the studies.

Surprisingly, the thiomethyl ester did not have an impact on the activity of yatakemycin or its analogs; however, the thiomethyl ester of duocarmycin SA showed a 2-fold improvement of cytotoxic activity.

Additional studies regarding the importance of both halves of these “sandwhich” DNA alkylating agents, the effects of the presence/absence of the thiomethyl ester, and further evaluation of new analogs are to be performed in future work.